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REMARKS

This amendment responds to the final office action mailed October 14, 2003. Prior to entry of this amendment, claims 38-88 were pending in the instant Application. With this amendment, claims 38-40, 44, 49, 50, 59-65, 71, 73-75, 77, 79-83, and 85 are amended, and claim 72 is cancelled. Thus, following entry of this amendment, claims 38-71 and 73-88 will be pending and under consideration.

I. The Amendments to the Claims

The amendments to claims 38-40, 44, 49, 50, 59-65, 71, 73-75, 77, 79-83, and 85 are fully supported by the specification and the claims as originally filed, and thus do not present new matter. For the PTO's convenience, all references to the specification of the present application are to the numbered paragraphs of the version of application published as U.S. Patent Application Publication No. US 2002/0182592.

Support for the amendment to claim 38 can be found, for example, in claim 1 as originally filed and in the specification at page 12, paragraphs 175, 176, and 178. Support for the amendment to claim 73 can be found, for example, in claim 73 as previously pending and in the specification at page 12, paragraphs 175, 176, and 178. Support for the amendment to claim 81 can be found, for example, in claim 81 as previously pending and in the specification at page 12, paragraphs 175, 176, and 178. Support for the amendment to claim 83 can be found, for example, in claim 83 as previously pending and in the specification at page 12, paragraphs 175 and 178. Support for the amendment to claims 39, 49, 50, 75, 79, and 80, can be found in, for example, claims 39, 49, 50, 75, 79, and 80, respectively, as previously pending, and in the specification at page 12, paragraph 175. Support for the amendment to claims 40, 44, 59-65, and 85 can be found, for example, in claims 40, 44, 59-65, 77, and 85, respectively, as previously pending, and in the specification at page 12, paragraph 178. Support for the amendment to claims 71, 87, and 88 can be found, for example, in claims 71, 87, and 88, respectively, as previously pending, and in the specification at page 12, paragraphs 175 and 178. Finally, support for the amendment to claims 74 and 82 may be found, for example, in claims 74 and 82, respectively, as previously pending, and in the specification at paragraphs 175 and 178.

In view of the foregoing, Applicants respectfully submit that the amendments to claims 38-40, 44, 49, 50, 59-65, 71, 73-75, 77, 79-83, and 85 are fully supported by the specification and the claims as originally filed. Therefore, Applicants respectfully submit

that the amendments to these claims do not present new matter. Accordingly, Applicants respectfully request entry of the present amendment to the claims pursuant to 37 C.F.R. 1.111.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

II. The Amendments to the Specification

The specification has been amended to add Tables I-III to the text of the application immediately before the claims. Versions of Tables I-III were filed together with the present application, and therefore the amendment to add Tables I-III to the end of the specification does not present new matter. For the PTO's convenience, copies of Tables I-III as filed with the present application are attached hereto as *Exhibit A*. Applicants believe that these Tables I-III should also have been published as part of the instant application; however, Tables I-III do not appear to be part of the published version of this application. In any event, Applicants wish to replace the as-filed versions of Tables I-III with the versions that appear above, and since, as shown above, Tables I-III were part of the present application as filed, the amendment to add Tables I-III to the end of the specification does not present new matter. Accordingly, Applicants respectfully request entry of the amendment to the specification under 37 C.F.R. § 1.111.

III. The Rejection of Claims 38-71 and 73-88 under 35 U.S.C. § 112, First Paragraph

Claims 38-71 and 73-88 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description and enablement requirements. In particular, the PTO alleged that a method that recites, *inter alia*, a viral construct comprising the patient-derived envelope protein and nucleic acids is not described or enabled by the specification. Without agreeing to the propriety of the rejection and solely to expedite prosecution of the claims, Applicants respectfully submit that the rejections are moot in view of the amendments to claims 38-71 and 73-88. None of claims 38-71 or 73-88 presently recites that the viral particles comprise an envelope protein and a nucleic acid encoding the envelope protein. Accordingly, Applicants respectfully request that the rejections for lack of written description and enablement under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. The Rejection of Claim 72 under 35 U.S.C. § 112, Second Paragraph

Claim 72 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Without agreeing to the propriety of the rejection, and solely to expedite prosecution of the claims, Applicants respectfully submit that the rejection is moot in view of the cancellation of claim 72. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 72 as indefinite under 35 U.S.C. § 112, second paragraph.

V. The Rejection of Claim 72 under 35 U.S.C. § 102(b)

Claim 72 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Petropoulos *et al.*, 2000, *Antimicrob. Agents Chemother.* 44:920-928. Without agreeing to the propriety of the rejection, and solely to expedite prosecution of the claims, Applicants respectfully submit that the rejection is moot in view of the cancellation of claim 72. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 72 as anticipated under 35 U.S.C. § 102(b).

VI. The Obviousness Rejection under 35 U.S.C. § 103(a)

In the first Office Action mailed January 28, 2003, claims 1-28 and 31-33 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Gao *et al.*, 1996, *Journal of Virology*, 70:1651-1667 ("Gao") and Petropoulos *et al.*, 2000, *Antimicrob. Agents. Chemother.*, 44:920-928 ("Petropoulos") in view of Grovit-Ferbas *et al.*, 1998, *Journal of Virology*, 72:8650-8658 ("Grovit") and Trkola *et al.*, 1999, *Journal of Virology*, 73:8966-8974 ("Trkola"). This rejection was withdrawn in the final Office Action mailed October 14, 2003, in view of the amendments to the claims filed September 19, 2003, which amended the claims to recite, *inter alia*, that the viral particles comprise envelope proteins and nucleic acids encoding the envelope proteins. The PTO indicated that amending the claims to delete this recitation would cause reinstatement of the art rejection set forth above. Applicants would like to thank the PTO for this indication and the opportunity to address the rejection prior to its reinstatement. Specifically, Applicants respectfully submit that the PTO cannot establish *prima facie* obviousness of claims 38-71 and 73-88 as presently pending in view of the cited references, since none of the references, either alone or in combination, teaches or suggests each and every element of the invention recited by claims 38-71 and 73-88.

A. *The Legal Standard*

To reject a claim under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51 U.S.P.Q.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. *The Cited References Do Not Teach or Suggest Each Element of the Invention as Presently Claimed*

Claims 38, 73, and 81 each recite a method that comprises a step wherein a plurality of viral particles are contacted with either a plurality of cells, as in claim 38, or a sample of cells, as in claims 73 and 81. In each of claims 38, 73, and 81, the viral particles that are

contacted to the cells comprise a plurality of envelope proteins derived from the population of viruses infecting a patient. Such a viral population infecting a patient usually comprises more than one quasispecies of, for example, HIV, where the individual quasispecies have different genotypes and phenotypes. In the case of HIV, for example, a patient infected with HIV is, in fact, infected with a population of HIV viruses where the individual members of the population have, for example, different *env* genes that encode envelope proteins with different structural and functional properties. None of Gao, Petropoulos, Trkola, or Grovit teaches or suggests any methods that use in a single assay viral particles that comprise a plurality of structurally distinct envelope proteins, let alone derived from a viral population infecting a patient. As such, none of the references, either alone or in combination, can render obvious the methods recited in the currently pending claims.

First, Gao neither teaches nor suggests any methods that use viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. Rather, Gao teaches a single-round virus infectivity assay using envelope proteins derived from single viral isolates. Whatever the source of the HIV *env* gene used to express the envelope proteins of these assays (most appear to be from viruses collected to represent potential vaccine evaluation sites), none of the assays tests proteins expressed from more than one envelope gene isolated from a single patient.

In particular, Gao focuses on validating the infectivity assay using single clones and the molecular genetics of the individual envelope proteins in such single clones. Nowhere does Gao teach a single-round infectivity assay that uses viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. In the assays described by Gao, nucleic acids corresponding to the envelope region of HIV were amplified in a PCR reaction, visualized by agarose gel electrophoresis, and cloned into pCRII vectors. *See* Gao *et al.* at page 1652, last full paragraph and paragraph bridging pages 1652-1653. These PCR products were then recloned into pSVIII*env* vectors for use in the single-round infectivity assays. *See* Gao *et al.* at page 1654, third full paragraph. Each clone was tested individually for the ability to express a functional envelope protein in the infectivity assay. *See* Gao *et al.* at page 1654, fourth full paragraph and at Table 2. Further, Gao does not suggest that its single-round infectivity assay could be modified to use a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. Since Gao does not teach or suggest a method that uses a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population

infecting a patient, Applicants respectfully submit that Gao does not teach or suggest this element of the methods of Claims 38, 73, and 81.

Similarly, Trkola also does not teach or suggest a method that uses a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. Instead, Trkola teaches a cell-based infectivity assay to assess infection by single viral strains of particular cell lines. Indeed, the whole point of Trkola is to describe a new cell line that is purportedly better for neutralization or infectivity assays. *See* Trkola *et al.* at page 891, Col. 1, first full paragraph. The viral strains used in the infectivity or neutralization assays are derived from single viral isolates that comprise a single envelope protein, and not a plurality of envelope proteins derived from a population of viruses infecting a patient. *See* Trkola *et al.* at page 8967, Col. 1, second and third full paragraphs. Thus, Trkola does not teach a method that uses a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. Trkola also contains no suggestion that its assays could be modified to use a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. Accordingly, Applicants respectfully submit that Trkola neither teaches nor suggests any methods that use a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient, as recited by Claims 38, 73, and 81.

Like Trkola and Gao, Grovit also does not teach or suggest a method that uses a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. Grovit instead characterizes individual envelope proteins cloned from a patient infected with a slow-progressing strain of HIV-1. In particular, Grovit describes cloning of the *env* gene from this strain of HIV-1 and characterization of the growth of recombinant HIV comprising this *env* gene. *See* Grovit-Ferbas *et al.* at page 8651, Col 1., first full paragraph, through the paragraph bridging Col. 1 and Col. 2 on page 8651. In the experiments to characterize the recombinant HIV clones, Grovit tests the growth of these cloned strains individually rather than in combination. *See* Grovit-Ferbas *et al.* at page 8652, Col. 2, first full paragraph. Thus, Grovit never contacts a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient with a sample or plurality of cells. Further, Grovit contains no suggestion that its methods could be adapted to use a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient. Accordingly, Applicants

respectfully submit that Grovit cannot teach or suggest a method that uses a plurality of viral particles that comprise a plurality of envelope proteins derived from a viral population infecting a patient, as recited by claims 38, 73, and 81.

Finally, these deficiencies of Gao, Trkola, and Grovit are not remedied by Petropoulos. As noted by the PTO, Petropoulos "does not teach analyzing patient derived *env* segment for their ability to infect new cells and for compounds that may inhibit virus entry." *See* Office Action mailed January 28, 2003, at page 10. Since Petropoulos does not teach analyzing even individual *env* segments, or an envelope protein expressed from an individual *env* segment, Petropoulos cannot possibly teach or suggest a method that uses viral particles that comprise a *plurality* of envelope proteins from a population of viruses infecting a patient. Accordingly, Applicants respectfully submit that Petropoulos, like Gao, Trkola, and Grovit, does not teach or suggest a method that uses viral particles that comprise a plurality of envelope proteins from a population of viruses infecting the patient as recited by claims 38, 73, and 81.

To sum up, Applicants respectfully submit that the PTO cannot establish *prima facie* obviousness of claims 38, 73, and 81 over Gao, Petropoulos, Trkola, and/or Grovit, since none of these references, either alone or in combination, teach or suggest a method that uses viral particles that comprise a plurality of envelope proteins from a population of viruses infecting the patient. Further, Applicants note that each of claims 39-71, 74-80, and 82-88 depend from one of claim 38, 73, or 81, and therefore also recite a method that uses viral particles that comprise a plurality of envelope proteins from a population of viruses infecting the patient. Accordingly, Applicants respectfully submit that claims 38-71 and 73-88 are not obvious under 35 U.S.C. § 103(a) over the cited references, either alone or in combination.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that claims 38-71 and 73-88 satisfy all the criteria for patentability and are in condition for allowance. Applicants respectfully request that the Examiner reconsider this application with a view towards allowance and solicit an early passage of claims 38-71 and 73-88 to issuance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Pursuant to 37 CFR § 1.136(a)(3), the Commissioner is hereby authorized to charge all required fees, including fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Jones Day Deposit Account No. 503013 (order no. 101920-999050).

Respectfully submitted,

Date: April 13, 2004

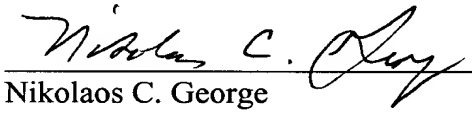

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Table 1

Cells

Cell	Receptor
5.25	CXCR4, CD4, CCR5 (not expressed well) BONZO
5.25.Luc4.M7	CD4, CCR5, BONZO
HOS.CD4.CCR5	CD4, CCR5
HOS.CD4.CXCR4	CD4, CXCR4
HOS.CD4	CD4, low level expression of CCR5 and CXCR4
HOS HT4 R5 GFP wt	CD4, CXCR4, CCR5
HOS.CD4.CCR5.GFP.M7#6*	CD4, CXCR4, CCR5
P4.CCR5	CD4, CXCR4, CCR5
U87.CD4	CD4
U87.CD4 R5	CD4, CCR5
U87.CD4 X4	CD4, CXCR4
MT2	CD4, CXCR4
MT4	CD4, CXCR4
PM1	CD4, CXCR4, CCR5
CEM NKr CCR5	CD4, CXCR4, CCR5

Table 2 Representative viruses and reagents

Viruses	Envelope[a]	Source
89.6, SF2	R5-X4/SI/B	ARRRP[B]
92BR014,92US076	R5-X4/SI/B	ARRRP
JR-CSF, 91US005	R5/NSI/B	ARRRP
91US054	SI/B	ARRRP
NL43, MN, ELI	X4/B	ARRRP
92HT599	X4	ARRRP
92UG031	R5/NSI/A	ARRRP(IN-HOUSE)
92TH014, 92TH026	R5/NSI/B	ARRRP(IN-HOUSE)
92BR025, 93MW959	R5/SI/C	ARRRP(IN-HOUSE)
92UG035	R5/NSI/D	ARRRP(IN-HOUSE)
92TH022, 92TH023	R5/NSI/E	ARRRP(IN-HOUSE)
93BR020	R5-X4/SI/F	ARRRP(IN-HOUSE)
Antibodies	**Epitope**	**SOURCE**
Mabs 2F5, 1577	gp41 TM	ARRRP
Mabs IG1b12, 2G12, 17b, 48D	gp120 SU	ARRRP
Neutralization sera #2, HIV-IG	Polyclonal	ARRRP
Entry inhibitors	**Target**	**Source**
CD4-IG	gp120 SU	Genentech
CD4-IGG2	gp120 SU	Adarc
SCD4	Sigma	Progenics
T20 (DP178)	gp41 TM	Trimeris
Rantes, MIP1a/b	CCR5	SIGMA/ARRRP
SDF1a/b	CXCR4	SIGMA/ARRRP
AMD 3100	CXCR4	AnorMed
Dextran sulfate, Heparin	Non-specific	Sigma

[a]R5 (CCR5 co-receptor), X4 (CXCR4 co-receptor) SI (syncytium inducing), NSI (non-syncytium inducing), A,B,C,D,E,F (envelope clade designation)

[b]AIDS Research and Reference Reagent Program

Table 3

Primers Tested for the Amplification of HIV Envelope	
RT PRIMERS	
RT env_N3	5'-GGA GCA TTT ACA AGC AGC AAC ACA GC-3'
RT env 9720	5' -TTC CAG TCA VAC CTC AGG TAC-3'
RT env 9740	5'-AGA CCA ATG ACT TAY AAG G-3'
5' PCR PRIMERS	
5'env	5' -GGG CTC GAG ACC GGT CAG TGG CAA TGA GAG TGA AG- 3'
5'env_Xho/Pin	5'-GGG CTC GAG ACC GGT GAG CAG AAG ACA GTG GCA ATG A-3'
5'env_START	5'-GGG CTC GAG ACC GGT GAG CAG AAG ACA GTG GCA ATG -3'
3' PCR PRIMERS	
3' env	5' -GGG TCT AGA ACG CGT TGC CAC CCA TCT TAT AGC AA- 3'
3'env_Xba/Mlu	5'-GGG TCT AGA ACG CGT CCA CTT GCC ACC CAT BTT ATA GC-3'
3'env_STOP	5'-GGG TCT AGA ACG CGT CCA CTT GCC ACC CAT BTT A-3'
3' delta CT	5' -GAT GGT CTA AGA CGC TGT TCA ATA TCC CTG CCT AAC TC- 3'
All Experiments are located in Virologic Book number 0188	